

reference. Accordingly, Applicants contend that they have satisfied all of the requirements under 35 U.S.C. 119(b).

4-5. The drawings are objected to due to several informalities. Applicants submit herewith formal drawings which are believed to obviate the Examiner's objections. Reconsideration and withdrawal of this objection is respectfully requested.

6-7. The disclosure is objected to because of several informalities. Applicants' amendments to the specification are believed to correct these informalities and obviate the objections.

8. Claims 10 and 11 are objected to for failing to present sequence identifiers in compliance with the rules as set forth in MPEP 2422.03. Applicants have amended the claims to provide proper sequence identifiers thus obviating the objection. Applicants' amendments are made solely to comply with the rules for presenting sequence identifiers and do not narrow the scope of the claims.

9. Claims 17 and 22 are objected to under 37 CFR 1.75(c) for allegedly failing to be in proper dependent form. Cancellation of claim 22 renders objection to that claim moot. Applicants' amendment of claim 17 is believed to obviate the objection. Reconsideration and withdrawal are respectfully requested.

10. Claims 10-12 are rejected under 35 U.S.C. 101 because the claims are allegedly directed to non-statutory subject matter. To expedite prosecution, Applicants have amended the claims to explicitly point out that the claimed polypeptides are purified polypeptides. Such amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

11-12. Claims 10-12, 17 and 22 are rejected under 35 U.S.C. 101 because the claimed invention allegedly lacks an apparent or disclosed specific and substantial credible utility. The claims are additionally rejected under 35 U.S.C. 112, first paragraph. Specifically, the Office Action contends that since the claimed invention is allegedly not supported by either a clear asserted utility or a well established utility then one of skill in the art would not know how to use the

claimed invention. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

Applicants direct the Examiner's attention to the "Revised Interim Utility Guidelines Training Materials". Specifically, Applicants contend that the claimed subject matter corresponds to Example 10 (pages 53-55) provided in these Training Materials. We believe that Example 10 corresponds directly to Applicants' disclosure. We also enclose further informatics work to clarify the extent of similarity between ZGGBP-1 and other genes (Enclosed herewith as Exhibits 1-3). Not only do these Exhibits provide information regarding the degree of sequence similarity between the claimed polypeptides and known proteins, but this data also more explicitly points out the important functional domains which are very highly conserved between ZGGBP-1 and other members of the family.

Specifically, Applicants provide a novel gene (ZGGBP-1) having SEQ ID NO: 1, which encodes a protein having SEQ ID NO: 2. An alignment of SEQ ID NO: 2 with known amino acid sequences reveals a high level of sequence conservation with NED-4. A BlastX sequence similarity search using the ZGGBP-1 nucleic acid sequence identified a number of closely related proteins, which are listed in Exhibit 1. Related amino acid sequences are members of the E3 ubiquitin protein ligase family. The results below confirm that SEQ ID NO: 2 has high homology to the human and mouse forms of NEDD-4. The next highest levels of homology at lower thresholds are identified with other members of the E3 Ubiquitin protein ligase family including Pub1. The function of E3 Ubiquitin ligases is well known in the art, and there is no reason to doubt the utility of the claimed invention.

Members of this family are typically identified by a number of functional domains including a C2 (Ca²⁺/lipid binding) domains, a HECT (Homologous to the E6-AP Carboxyl Terminus) ubiquitin-protein ligase domain and several WW domains involved in protein-protein interactions. Analysis using Hmm against Pfam motifs identifies a number of conserved functional domains (Exhibit 2). These domains shows the functional features typically associated with members of the NEDD4 family. An alignment of ZGGBP-1 to the human and mouse forms of NEDD-4 reveal striking homologies over the functional domains of the protein.

Exhibit 3 illustrates the functional motifs identified for NEDD-4. For clarity, the domains are highlighted in green for NEDD-4 and in red for ZGGBP-1.

Functional studies carried out on members of the NEDD4 family indicate that they have ubiquitin protein ligase activity (Staub *et al* 1996; Abriel *et al* 2000; Springael *et al* 1999, enclosed herewith as Exhibits 4-6). The WW domains of the NEDD4 gene family have been demonstrated to interact with the epithelial sodium channel (ENaC) through the proline-rich motifs within the C termini of the ENaC subunits and thereby to downregulate the intracellular Na⁺ concentration (Staub *et al* 1997; Schild *et al* 1996; Abreil *et al* 1999; Harvey *et al* 1999; Synder *et al* 2001, enclosed herewith as Exhibits 7-11). There is also evidence that these domains can bind to phosphoserine and phosphothreonine residues (Lu *et al* 1999, enclosed herewith as Exhibit 12) thus indicating that members of the NEDD-4 family may be able to interact with a larger repertoire of protein substrates than first thought. The C2 domain has been shown to mediate Ca²⁺-dependant plasma membrane localisation of the protein via phospholipid binding (Plant *et al* 1997, enclosed herewith as Exhibit 13).

The question when determining the utility of a claimed invention is whether, "based on the record, [is] there is a 'well established utility' for the claimed invention?" (Revised Interim Utility Guidelines Training Materials, page 54). Furthermore, the Guidelines instruct that "if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed." (page 55). Applicants contend that given the sequence and structural conservation between the claimed polypeptides and E3 Ubiquitin ligases known in the art, substantial and credible utility of the claimed invention would have been readily apparent to one of skill in the art.

We claim a purified polypeptide comprising SEQ ID NO: 2. Based upon the disclosure of the specification and the enclosed informatics work, there is clearly a well-established utility for the invention. The Office Action has raised no reason to doubt that SEQ ID NO: 2 is a protein that is a E3 ubiquitin protein ligase and has a specific, substantial and credible utility based upon its ubiquitin protein ligase activity. Accordingly, Applicants have satisfied the requirements under 35 U.S.C. 101. Reconsideration and withdrawal of the rejection are respectfully requested.

13. Claims 10-12, 17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants contend that the claims are enabled throughout their scope. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more explicitly point out the claimed subject matter. Applicants' amendments are not in acquiescence of the Examiner's rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

14-16. Claims 10-12, 17 and 22 are rejected under 35 U.S.C. 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. To expedite prosecution, Applicants have amended the claims to more explicitly point out the claimed subject matter. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are requested.

17. Claim 10 is rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Hillier et al. Applicants note that claim 10 was amended to overcome the rejection under 35 U.S.C. 112, second paragraph, and that such an amendment obviates the rejection under 35 U.S.C. 102(b). Reconsideration and withdrawal of the rejection are requested.

18. Claim 11 is rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Marra et al. Applicants note that claim 11 was amended to overcome the rejection under 35 U.S.C. 112, second paragraph, and that such an amendment obviates the rejection under 35 U.S.C. 102(b). Reconsideration and withdrawal of the rejection are requested.

19. Applicants note with appreciation the Examiner's recommendation regarding the recitation of the term "fragment thereof".

20. Claim 12 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Karin et al. As outlined above, claims 10-12 were amended in order to address the Examiner's rejection under 35 U.S.C. 112, second paragraph. Applicants' amendments are also believed to obviate

the rejection under 35 U.S.C. 103(a). Reconsideration and withdrawal of this rejection are requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Respectfully Submitted,

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